

REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed in patent number _____, granted _____, and for which a reissue patent is sought on the invention entitled _____,

the specification of which

☒ is attached hereto.

☐ was filed on _____ as reissue application number _____ / _____
and was amended on _____
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing.

☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

☐ by reason of other errors.

At least one error upon which reissue is based is described as follows:

Patentee claimed less than he had the right to claim in U.S.P. 6,303,146. Claims 1-10 of the latter recite certain particle size distributions of glibenclamide in solid oral dosage forms and pharmaceutical compositions (including tablets), which also contain metformin, as well as methods of using these. The bioavailability of glibenclamide from such combination pharmaceutical compositions and dosage forms is comparable to the glibenclamide bioavailability attained with separate administrations of metformin and glibenclamide. However, achievement of such comparable glibenclamide bioavailability in general (without reference to particle size distribution) is also an invention disclosed in the patent specification. See, for example, column 2, lines 41-44 of U.S.P. 6,303,146:

The present invention provides in particular a tablet comprising a combination of metformin and glibenclamide, exhibiting a comparable glibenclamide bioavailability to the co-administered tablets.

Corresponding new claims are added herein (claims 11-40).

In addition, an obvious error in claim 5 of the patent is being corrected by inserting the missing reference to parent claim 4. This corrects the error of ostensibly claiming in claim 5 more than patentee had the right to claim. Claim 3 is also amended by correcting the typographical error (replacing "60" by "40"). A new dependent claim 41 is also added.

(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)

Docket Number (Optional)

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Name(s)

Registration Number

Correspondence Address: Direct all communications about the application to:

☒ Customer Number

OR

Type Customer Number here



23599

PATENT TRADEMARK OFFICE

☐ Firm or Individual Name

Millen, White, Zelano & Branigan, P.C.

Address

Address

City

Arlington

State

VA

ZIP

22201

Country

Telephone

(703) 243-6333

Fax

(703) 243-6410

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of sole or first inventor (given name, family name)

YVES BONHOMME

Inventor's signature

Residence

Charbonnieres Les Bains, France

Date

13. x 11. 2002

Mailing Address

Le Buclay - 21 avenue de la Paix - 69260 Charbonnieres Les Bains, France

Citizenship

Full name of second joint inventor (given name, family name)

Inventor's signature

Date

Residence

Aylesbury - Buckingham Shire HP 21 9UT, Great Britain

Citizenship

GREAT BRITAIN

Mailing Address 48 Langdon Avenue, Aylesbury - Buckingham Shire HP 21 9UT, Great Britain

Full name of third joint inventor (given name, family name)

Inventor's signature

Date

Residence

Flintshire, United Kingdom

Citizenship


GREAT BRITAIN

Mailing Address

Ben Rhydding, Church Lane, Rhydymwyn, Mold, Flintshire CH7 5XZ, United Kingdom

☒ Additional joint inventors are named on separately numbered sheets attached hereto.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 3)						Docket Number (Optional)					
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<p>Correspondence Address: Direct all communications about the application to:</p> <p><input checked="" type="checkbox"/> Customer Number →</p> <p style="margin-left: 150px;">OR Type Customer Number here</p>											
<div style="display: inline-block; text-align: left;"> 23599 <small>PATENT TRADEMARK OFFICE</small></div>											
<input checked="" type="checkbox"/> Firm or Individual Name		Millen, White, Zelano & Branigan, P.C.									
Address											
Address											
City		Arlington		State		VA		ZIP		22201	
Country		U.S.A.									
Telephone		(703) 243-6333				Fax		(703) 243-6410			
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Full name of sole or first inventor (given name, family name)											
Inventor's signature											
Residence Cheshire WA 69 PE Great Britain						Date					
Mailing Address 4 Redstone Hill - Helsby - Cheshire WA 69 PE - Great Britain						Citizenship GREAT BRITAIN					
Full name of second joint inventor (given name, family name)											
Inventor's signature						Date					
Residence						Citizenship					
Mailing Address											
Full name of third joint inventor (given name, family name)											
Inventor's signature						Date					
Residence						Citizenship					
Mailing Address											
<input type="checkbox"/> Additional joint inventors are named on separately numbered sheets attached hereto.											

REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)
MERCK-2593 R1

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is described and claimed in patent number U.S. 6,303,146, granted October 16, 2001, and for which a

reissue patent is sought on the invention entitled SOLID ORAL DOSAGE FORM COMPRISING A COMBINATION OF METFORMIN AND GLIBENCLAMIDE,

the specification of which

☒ is attached hereto.

☐ was filed on _____ as reissue application number _____ /
and was amended on _____
(If applicable)

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

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☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.

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The present invention provides in particular a tablet comprising a combination of metformin and glibenclamide, exhibiting a comparable glibenclamide bioavailability to the co-administered tablets.

Corresponding new claims are added herein (claims 11-40).

In addition, an obvious error in claim 5 of the patent is being corrected by inserting the missing reference to parent claim 4. This corrects the error of ostensibly claiming in claim 5 more than patentee had the right to claim. Claim 3 is also amended by correcting the typographical error (replacing "60" by "40"). A new dependent claim 41 is also added.

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Name(s) Anthony J. Zelano			Registration Number 27,969			
Correspondence Address: Direct all communications about the application to:						
<input checked="" type="checkbox"/> Customer Number			<div style="border: 1px solid black; width: 150px; height: 1.2em;"></div>		<div style="border: 1px solid black; padding: 5px; text-align: center;"> 23599 PATENT TRADEMARK OFFICE</div>	
OR			Type Customer Number here			
<input type="checkbox"/> Firm or Individual Name		Millen, White, Zelano & Branigan, P.C.				
Address						
Address						
City	Arlington	State	VA	ZIP	22201	
Country						
Telephone	(703) 243-6333		Fax	(703) 243-6410		
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.						
Full name of sole or first inventor (given name, family name) Yves BONHOMME						
Inventor's signature						
Residence Charbonnieres Les Bains, France			Date			
Mailing Address Le Bucly - 21 avenue de la Paix - 69260 Charbonnieres Les Bains, France			Citizenship FRANCE			
Full name of second joint inventor (given name, family name) Geoffrey NICHOLSON						
Inventor's signature 			Date 16.12.02			
Residence Aylesbury - Buckingham Shire HP 21 9UT, Great Britain			Citizenship GREAT BRITAIN			
Mailing Address 48 Langdon Avenue, Aylesbury - Buckingham Shire HP 21 9UT, Great Britain						
Full name of third joint inventor (given name, family name) Gillian CAVE						
Inventor's signature			Date			
Residence Flintshire, United Kingdom			Citizenship GREAT BRITAIN			
Mailing Address Ben Rhydding, Church Lane, Rhydymwyn, Mold, Flintshire CH7 5XZ, United Kingdom						
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OR Type Customer Number here			
<input checked="" type="checkbox"/> Firm or Individual Name Millen, White, Zelano & Branigan, P.C.			
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Full name of sole or first inventor (given name, family name) Sarah J. NICHOLSON			
Inventor's signature			
Residence Cheshire WA 69 PE Great Britain		Date	
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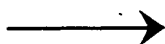


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Inventor's signature			
Residence Charbonnieres Les Bains, France	Date		
Mailing Address Le Bucday - 21 avenue de la Paix - 69260 Charbonnieres Les Bains, France	Citizenship FRANCE		
Full name of second joint inventor (given name, family name) Geoffrey NICHOLSON			
Inventor's signature		Date	
Residence Aylesbury - Buckingham Shire HP 21 9UT, Great Britain	Citizenship GREAT BRITAIN		
Mailing Address 48 Langdon Avenue, Aylesbury - Buckingham Shire HP 21 9UT, Great Britain			
Full name of third joint inventor (given name, family name) Gillian CAVE			
Inventor's signature 		Date 16th December 2002	
Residence Flintshire, United Kingdom	Citizenship GREAT BRITAIN		
Mailing Address Ben Rhydding, Church Lane, Rhydymwyn, Mold, Flintshire CH7 5XZ, United Kingdom			
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☒ Firm or Individual Name

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Full name of sole or first inventor (given name, family name)
Sarah J. NICHOLSON *out forth*

Inventor's signature

Sarah Nicholson

Residence
Cheshire WA 69 PE Great Britain

Date

17th December 2002

Mailing Address
4 Redstone Hill - Helsby - Cheshire WA 69 PE - Great Britain

Citizenship
GREAT BRITAIN

Full name of second joint inventor (given name, family name)

Inventor's signature

Date

Residence

Citizenship

Mailing Address

Full name of third joint inventor (given name, family name)

Inventor's signature

Date

Residence

Citizenship

Mailing Address

☐ Additional joint inventors are named on separately numbered sheets attached hereto.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re ReissueApplication of:

BOX REISSUE

Examiner: Unassigned

Serial No.: 10/329,426

Group Art Unit: 1615

Filed: December 27, 2002

U.S.P. No.: 6,303,146

Title:

**WRITTEN ASSENT OF THE ASSIGNEE; § 3.73(B) STATEMENT; AND OFFER TO
SURRENDER**

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The undersigned are authorized officials of the assignee corporation Merck Sante of
Lyons France, the successor in interest of the above captioned patent by virtue of:

1. An assignment from the inventors to LIPHA, recorded in the U.S. Patent and
Trademark Office on November 15, 1999, Reel 010369, Frame 0928, a copy attached as Exhibit
1;

2. The fact that at least as early as July 1, 1997, and continuing to Dec. 7, 2001 (see
below), LIPHA had an original formal corporate name of LIPHA S.A. (a public limited
company) as evidenced by the attached Extract from the commercial and companies register,
Management No.1992B00858 where the company LIPHA S.A. is mentioned on page 3, the third
from last line, Exhibit 2;

3. The fact that LIPHA S.A. on December 7, 2001 changed its corporate structure from a "société par actions simplifiée" abbreviated in France as S.A.S. (a simplified joint-stock company) without creating a new legal person, as seen from the attached copy of a legal notice from the Lyon business register, Exhibit 3; and

4. The fact that LIPHA S.A.S. on May 27, 2002 changed its name to Merck Sante as evidenced from the attached copy of a legal notice from the Lyon business register, Exhibit 4.

Exhibits 1, 2 and 3 are being concurrently tendered for recordation in the assignment branch of the United States Patent and Trademark Office.

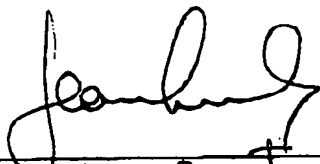
The undersigned authorized officials of Merck Sante having the power to consent to this reissue application, hereby assent to this reissue application in its entirety and offer to surrender the original patent.

Date

April 10, 2003

Name:

Title:


THOMAS J. ABEL
Chairman

Date

Name:

Title:

EXHIBIT 1

Atty Docket No.: 2685-0011-0

11-15-1999

FORM PTO-1595
1-31-92



U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

MRD 11-16-99

101199999

To the Honorable Commissioner of Patents and Trademarks. Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Yves BONHOMME, Geoffrey NICHOLSON, Gillian CAVE
and Sarah J. NICHOLSON

Additional name(s) of conveying party(ies) attached? ☐ Yes ☒ No

3. Nature of Conveyance:

- ☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other

Execution Date: October 20, 1999

2. Name and address of receiving party(ies):

Name: LIPHA

Address: 34 rue Saint-Romain 69008 LYON France



Additional name(s) and address(es) attached? ☐ Yes ☒ No

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is:

A. Patent Application No.(s)
09/353,141

B. Patent No.(s)

Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:

OBLON, SPIVAK, McCLELLAND, MAIER &
NEUSTADT, P.C.
Attorneys at Law
Fourth Floor
1755 Jefferson Davis Highway
Arlington, Virginia 22202

6. Total applications and patents involved: 1

7. Total fee (37 CFR 3.41): \$40.00

- ☒ Enclosed
☐ Authorized to be charged to deposit account

8. Deposit account number: 15-0030

(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Norman F. Oblon

Name of Person Signing

Registration Number: 24,618

FD Vastine

Signature

Frederick D. Vastine

Registration No. 27,013

11/10/99

Date

Total number of pages including this cover sheet: 3

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Mail documents to be recorded with required cover sheet information to:

Commissioner of Patents and Trademarks
Box Assignments
Washington, D.C. 20231

11/15/1999 DHSUYEN 00000051 09353141

01 FC:581

40.00 DP

PATENT
REEL: 010369 FRAME: 0927

Assignment Of Application

Page 1 of 2

WHEREAS, I (WE) 1/ BONHOMME Yves - 2/ NICHOLSON Geoffrey - 3/ CAVE Gillian -4/ NICHOLSON Sarah J.INSERT NAMES
AND RESIDENCE
ADDRESSES OF
THE INVENTORS:1/ Le Buclay - 21 Avenue de la Paix - 69260 CHARBONNIERES LES BAINS France2/ 48 Langdon Avenue - Aylesbury - BUCKINGHAM SHIRE HP 21 - 9 UT - Great Britain3/ 26 Hilbre Drive - ELLESMERE PORT CH 65 9JQ - Great Britain4/ 4 Redstone Hill - Helsby- CHESHIRE WA 69 PE Great Britain

, respectively.

INSERT TITLE
OF INVENTION:have invented certain new and useful improvements in: "Solid oral dosage form comprising a combination of metformin and glibenclamide".INSERT DATE IN-
VENTORS SIGNED
DECLARATION:for which an application for Letters Patent was executed on October 20, 1999(Application No. 09/353,141, filed July 14, 1999), andINSERT NAME
AND ADDRESS OF
COMPANY OR
OTHER ASSIGNEE:WHEREAS. LIPHA(hereinafter referred to as "ASSIGNEE") having a place of business at: 34, rue Saint-Romain
69008 LYON France

is desirous of acquiring the entire right, title and interest in and to said invention and in and to any Letters Patent that may be granted therefor in the United States and its territorial possessions and in any and all foreign countries;

NOW, THEREFORE, in consideration of the sum of FIVE DOLLARS (\$5.00), the receipt whereof is hereby acknowledged, and for other good and valuable consideration, I (WE), by these presents do sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof.

8/92

PATENT
REEL: 010369 FRAME: 0928

I (WE) hereby authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letters Patent, when granted, to said ASSIGNEE as the assignee of my (our) entire right, title and interest in and to the same, for the sole use and behoof of said ASSIGNEE, its (his) successors and assigns, to the full end of the term for which said Letters Patent may be granted, as fully and entirely as the same would have been held by me (us) had this Assignment and sale not been made.

Further, I (WE) agree that I (WE) will communicate to said ASSIGNEE or its (his) representatives any facts known to me (us) respecting said invention, and testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, substitute, renewal and reissue applications, execute all necessary assignment papers to cause any and all of said Letter Patent to be issued to said ASSIGNEE, make all rightful oaths, and, generally do everything possible to aid said ASSIGNEE, its (his) successors and assigns, to obtain and enforce proper protection for said invention in the United States and its territorial possessions and in any and all foreign countries.

The undersigned hereby grant(s) the firm of Oblon, Spivak, McClelland, Maier & Neustadt, P.C. of Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202 the power to insert on this assignment any further identification, including the application number and filing date, which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for recordation of this document.

Date: October 20, 1999

(Signature of Inventor)

BONHOMME Yves

Date: October 20, 1999

(Signature of Inventor)

NICHOLSON Geoffrey

Date: October 20, 1999

(Signature of Inventor)

CAVE Gillain

Date: October 20, 1999

(Signature of Inventor)

NICHOLSON Sarah J.

Date: _____

(Signature of Inventor)

Date: _____

(Signature of Inventor)

Date: _____

(Signature of Inventor)

Date: _____

(Signature of Inventor)

OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C.
ATTORNEYS AT LAW
FOURTH FLOOR
1755 JEFFERSON DAVIS HIGHWAY
ARLINGTON, VIRGINIA 22202

8/92

RECORDED: 11/10/1999

PATENT
REEL: 010369 FRAME: 0929

EXHIBIT 2

Extract from the commercial and companies register

REGISTRATION AND IDENTITY OF THE PERSON

registration number: 572 028 033 Lyons Commercial and Companies Register
- registration date : 19 March 1992
name : LIPHA
legal form : simplified joint-stock company ["société par actions simplifiée"]
duration of the legal person : 99 years

PARTICULARS OF THE ENTERPRISE

capital : 77,797,247.00 EUROS
registered office : 37 rue st Romain 69008 Lyons - FRANCE
This company already formed is transferring its registered office from PARIS 75006 49 Rue Saint André des Arts to LYONS 69008 34 Rue Saint Romain. The Company is not retaining any activity at its former registered office
principal activities of the enterprise : Studies and research in the fields of chemistry and pharmacy.
trade name : No trade name has been declared
financial year end-date : 31 December

DIRECTION, MANAGEMENT AND CONTROL

chairman Mr. TREILLES Jean Noel born on 20 October 1944 in TOULOUSE (31) - France - of French nationality
customary name : Mr. TREILLES Jean
legal address : 37 rue st Romain 69008 Lyons - FRANCE
general manager Mr. MEYNAUD André born on 23 February 1942 in LYON 6th district ["arrondissement"] (69) - France - of French nationality
customary name : Mr. MEYNAUD André
legal address : 37 rue st Romain 69008 Lyons - FRANCE
general manager Mr. BONHOMME Yves born on 02 May 1945 in CALUIRE (69) - France - of French nationality
customary name : Mr. BONHOMME Yves
legal address : 37 rue st Romain 69008 Lyons - FRANCE
supervisory board member Mr. MENU Gérard born on 01 February 1947 in CRETEIL (94) - France - of French nationality
customary name : Mr. MENU Gérard
legal address : 37 rue Saint Romain 69008 Lyons - FRANCE

The word "ORIGINAL" above means this is an original issued by the registry

supervisory board member

Mr. HEIMERMANN Marc born on 25 July 1945 in COLMAR (68) - France - of French
nationality
customary name : Mr. HEIMERMANN Marc
legal address : 37 rue Saint Romain 69008 Lyons - FRANCE

incumbent statutory auditor

KPMG DEPARTEMENT FIDUCIAIRE DE FRANCE - RESIDING
registered office : 45 rue Villiers 92200 Neuilly Sur Seine - FRANCE

alternate statutory auditor

JEAN CLAUDE ANDRE ET ASSOCIES - RESIDING
registered office : 2 b rue de Villiers 92200 Levallois Peret - FRANCE

PRINCIPAL PLACE OF BUSINESS

address :

activity carried on :

commencement date of operation :

origin :

Method of operation :

37 rue st Romain 69008 Lyons - FRANCE
Studies and research in the fields of chemistry and pharmacy
01 July 1991
creation
direct operation

SECONDARY PLACE OF BUSINESS

address :

activity carried on :

commencement date of operation :

origin :

method of operation :

10 avenue de Lattre de Tassigny Z.I. 69330 Meyzieu - FRANCE
Manufacture and storage of chemical and pharmaceutical products
31 December 1997
various
Partial contribution of assets
direct operation
Direct operation

SECONDARY PLACE OF BUSINESS

address :

activity carried on :

commencement date of operation :

origin :

method of operation :

115 avenue Lacassagne 69003 Lyons - FRANCE
Manufacture and sale of pharmaceutical products
01 January 1998
various
Partial contribution of assets
direct operation
Direct operation

DECLARATION OF EXTERNAL REGISTRATIONS

registration at the Orleans Commercial Court Registry under management number
1998B00049

registration at the Calais Commercial Court Registry under management number
1998B00023

registration at the Nanterre Commercial Court Registry under management number
1998B00817

The word "ORIGINAL" above means this is an original issued by the registry

DECLARATIONS AND OBSERVATIONS

Formation : Filing at the Paris Registry on 23/05/27
Notice : La Gazette du Palais [Court Gazette] of 24/05/27
Transfer decision : Filing at the Paris Registry
Notice : Law of 23/08/91
Transfer: Filing at the Lyons Registry of 19

AMENDING DECLARATION of 23 December 1997

Transfer of the registered office and Transfer of the principal place of business from 34 to 37
Rue St Romain 69008 LYONS, from 22/10/1997

AMENDING DECLARATION of 31 December 1997 :

Partial contribution of assets of the pharmaceutical branch of activity by the company MERCK
LIPHA S.A. the registered office of which is 37 Rue St Romain 69008 LYONS (777 335 340
LYONS COMMERCIAL AND COMPANIES REGISTER) to the Company LIPHA S.A. the
registered office of which is at 37 Rue St Romain 69008 LYONS (572 028 033) with retroactive
effect to 01/01/1997.

*Any amendment or falsification of this extract may lead to criminal prosecution.
Only the registrar is legally authorised to issue original signed extracts,
and any reproduction of this extract even certified to be a true copy, is without force.*

Extract certified to be a true copy

ISSUED in Lyons on 21/12/2001

The registrar

SEAL OF LYONS
COMMERCIAL
COURT

[Signed]

*The above translation in English is correct.
J. William Miller*

The word "ORIGINAL" above means this is an original issued by the registry

Extrait du registre du commerce et des sociétés

IMMATRICULATION ET IDENTITE DE LA PERSONNE

numéro d'immatriculation : 572 028 033 RCS Lyon
date d'immatriculation : 19 mars 1992
dénomination : LIPHA
forme juridique : société par actions simplifiée
durée de la personne morale : 99 années

CARACTERISTIQUES DE L'ENTREPRISE

capital : 77 797 247,00 EUROS
siège social : 37 rue st Romain 69008 Lyon - FRANCE
Cette société déjà constituée transfère son siège social de PARIS 75006 49 Rue Saint André des Arts à LYON 69008 34 Rue Saint Romain. La société ne conserve aucune activité à l'ancien siège so
activités principales de l'entreprise : Etudes et recherche dans les domaines de la chimie et de la pharmacie.
nom commercial : il n'est pas déclaré de nom commercial
date de clôture de l'exercice : 31 Décembre

DIRECTION, ADMINISTRATION, CONTRÔLE

président : Monsieur TREILLES Jean Noel né(e) le 20 octobre 1944 à TOULOUSE (31) - France - de nationalité française
nom d'usage : Monsieur TREILLES Jean
domicilié(e) : 37 rue st Romain 69008 Lyon - FRANCE

directeur général : Monsieur MEYNAUD Andre né(e) le 23 février 1942 à LYON 6 arrdt. (69) - France - de nationalité française
nom d'usage : Monsieur MEYNAUD Andre
domicilié(e) : 37 rue st Romain 69008 Lyon - FRANCE

directeur général : Monsieur BONHOMME Yves né(e) le 02 mai 1945 à CALUIRE (69) - France - de nationalité française
nom d'usage : Monsieur BONHOMME Yves
domicilié(e) : 37 rue st Romain 69008 Lyon - FRANCE

membre du conseil de surveillance : Monsieur MENU Gérard né(e) le 01 février 1947 à CRETEIL (94) - France - de nationalité française
nom d'usage : Monsieur MENU Gérard
domicilié(e) : 37 rue Saint Romain 69008 Lyon - FRANCE

Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe

membre du conseil de surveillance Monsieur HEIMERMANN Marc né(e) le 25 juillet 1945 à COLMAR (68) - France - de nationalité française
nom d'usage : Monsieur HEIMERMANN Marc
domicilié(e) : 37 rue Saint Romain 69008 Lyon - FRANCE

commissaire aux comptes titulaire KMPG DEPARTEMENT FIDUCIAIRE DE FRANCE - DMT
siège social : 45 rue Villers 92200 Neuilly Sur Seine - FRANCE

commissaire aux comptes suppléant JEAN CLAUDE ANDRE ET ASSOCIES - DMT
siège social : 2 b rue de Villiers 92200 Levallois Perret - FRANCE

ETABLISSEMENT PRINCIPAL

adresse : 37 rue st Romain 69008 Lyon - FRANCE
activité exercée : Etudes et recherche dans les domaines de la chimie et de la pharmacie.
date de début d'exploitation : 01 juillet 1991
origine : création
Mode d'exploitation : exploitation directe

ETABLISSEMENT SECONDAIRE

adresse : 10 avenue de Lattre de Tassigny Zi 69330 Meyzieu - FRANCE
activité exercée : Fabrication et stockage de produits chimiques et pharma- ceutiques
date de début d'exploitation : 31 décembre 1997
origine : divers
Apport partiel d'actif
mode d'exploitation : exploitation directe
Exploitation directe

ETABLISSEMENT SECONDAIRE

adresse : 115 avenue Lacassagne 69003 Lyon - FRANCE
activité exercée : Fabrication et vente de produits pharmaceutiques
date de début d'exploitation : 01 janvier 1998
origine : divers
Apport partiel d'actif
mode d'exploitation : exploitation directe
Exploitation directe

MENTION DES IMMATRICULATIONS EXTERIEURES

immatriculation au Greffe du Tribunal de Commerce d'Orléans sous le numéro de gestion 1998B00049

immatriculation au Greffe du Tribunal de Commerce de Calais sous le numéro de gestion 1998B00023

Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe.

immatriculation au Greffe du Tribunal de Commerce de Nanterre sous le numéro de gestion
1998B00817

MENTIONS ET OBSERVATIONS

Constitution : Dépôt au Greffe de Paris le 23/05/27
Publicité : La Gazette du Palais du 24/05/27
Décision de transfert : Dépôt au Greffe de Paris
Publicité : La Loi du 23/08/91
Transfert : Dépôt au Greffe de Lyon du 19

DECLARATION MODIFICATIVE du 23 Décembre 1997
Transfert du siège social et Transfert du principal établissement du
34 au 37 Rue St Romain 69008 LYON, à compter du 22/10/1997
DECLARATION MODIFICATIVE du 31 Décembre 1997 :
Apport partiel d'actif de la branche d'activité pharmaceutique par la
société MERCK LIPHA S.A. dont le siège social est 37 Rue St Romain
69008 LYON (777 335 340 RCS LYON) à la société LIPHA S.A. dont le
siège social est 37 Rue St Romain 69008 LYON (572 028 033) avec effet
rétroactif au 01/01/1997.

*Toute modification ou falsification du présent extrait expose à des poursuites pénales
Seul le greffier est légalement habilité à délivrer des extraits signés en original,
toute reproduction du présent extrait même certifiée conforme est sans valeur.*

Pour extrait certifié conforme

DELIVRE à Lyon le 21/12/2001

Le greffier



Le mot "ORIGINAL" ci-dessus signifie que vous êtes en présence d'un original émanant du greffe

EXHIBIT 3

LIPHA SA

simplified joint-stock company ["société par actions simplifiée"]
with a capital of € 77,797,247

Registered office : 37 rue Saint-Romain, 69008 Lyons
572 028 033 Lyons Commercial and Companies Register

There emerges from the deliberations of the extraordinary general meeting of 7 December 2001:

1) That the company was converted from a public limited company ["société anonyme"] into a simplified joint-stock company ["société par actions simplifiée"], without creating a new legal person, with adoption of new memorandum and articles of association, from 7 December 2001.

2) A change in the following declarations to be published:

Previous declarations	New declarations
-----------------------	------------------

FORM

Public limited company ["Société anonyme"].	Simplified joint-stock company ["Société par actions simplifiée"].
--	--

MANAGEMENT AND DIRECTION

Chairman and director : Mr.
Jean-Noël TREILLES.

Chairman: Mr. Jean-Noël
TREILLES, whose legal address
is 37, rue Saint-Romain, Lyons
8.

General managers:
Mr. André MEYNAUD.
Mr. Yves BONHOMME.

General managers:
Mr. André MEYNAUD whose
legal address is 37, rue Saint-
Romain, Lyons 8.
Mr. Yves BONHOMME whose
legal address is 37, rue Saint-
Romain, Lyons 8.

Directors:
Doctor Johannes
SOMBROEK.
Doctor Michaël ROMER.
Professor Doctor Bernhard
SCHEUBLE.

Supervisory Board:
Mr. Gérard MENU, whose legal
address is 37, rue Saint-Romain,
Lyons 8.
Mr. Marc HEIDERMANN,
whose legal address is 37, rue
Saint-Romain, Lyons 8.

Statutory Auditors:
- Incumbent: KPMG
DEPARTEMENT
FIDUCIAIRE DE FRANCE -
- Alternate : SCP Jean-Claude
ANDRE ET ASSOCIES -

Statutory Auditors:
- Incumbent: KPMG
DEPARTEMENT
FIDUCIAIRE DE FRANCE,
45, rue Villiers, 92200 Neuilly-
sur-Seine.
- Alternate : SCP Jean-Claude
ANDRE ET ASSOCIES 2 bis,
rue de Villiers
92200 Levallois-Peret.

Approval : Transfers of shares, even between members, shall be
subject to the prior approval of all the members.

Filed at the Lyons Commercial Court Registry.

Notice hereby given
The legal representative

BEST AVAILABLE COPY

*The above English
translation is correct.
J. William Miller*

- SOC 13900 -

**ATELIER COUTURE
DE LINGERIE
A.C.L.**

société anonyme au capital de 1 300 000 F
Siège social : 150 à 160, rue Lançon
69100 Villeurbanne
398 840 793 RCS Lyon

Aux termes d'une assemblée générale extraordinaire datée du 30 novembre 2001 les actionnaires de la société A.C.L. ont approuvé le projet de fusion établie le 10 novembre 2001 prévoyant l'absorption de la société A.C.L. la société BELLANGER PERRET ET CIE - B.P.C., à responsabilité limitée au capital de 4 888 000 F, le siège social est sis 150 à 160, rue Lançon, 69100 Villeurbanne, immatriculée au RCS de Lyon sous le n° 12 467 532.

En conséquence, l'assemblée générale a décidé la dissolution anticipée, sans liquidation de la société A.C.L., passif étant pris en charge par la société absorbante, les parts émises par cette dernière au titre de la fusion ne sont pas directement attribuées aux actionnaires de la société absorbée.

L'assemblée générale extraordinaire des actionnaires de la société BELLANGER PERRET ET CIE - B.P.C. du 30 novembre 2001 ayant approuvé la fusion et cédé à l'augmentation corrélatrice de son capital, la fusion et la dissolution de la société A.C.L. sont devenues définitives à cette date.

Pour avis

- SOC 13898 -

SITES SN

société à responsabilité limitée au capital de 51 000 F
Siège social : 15, avenue Pierre-Allard, 69500 Bron
333 485 829 RCS Lyon

L'assemblée générale extraordinaire réunie en date du 12 décembre 2001 a décidé :

1) D'augmenter le capital social de 96 196,75 F pour le porter à 147 196,75 F par l'incorporation directe de réserves au capital, et élévation de la valeur nominale des parts existantes de 100 F à 288,621 F arrondie à 288,62 F ;

2) De convertir le capital social en euros qui s'élève à 140 €, divisé en 510 parts de 44 € ;

3) De modifier en conséquence l'article 7 des statuts.

La gérance

- SOC 13717 -

FREDERIQUE BUFFIN

société en nom collectif au capital de 31 400 €
Siège social : 6, rue Pizay, 69001 Lyon
433 080 082 RCS Lyon

Suite aux délibérations de l'AGE du 14 décembre 2001, il a été décidé la dissolution anticipée et amiable de la société.

Il a été nommé en qualité de liquidateur amiable :

Mademoiselle Frédérique BUFFIN, demeurant à Seppe (38780), « Garenne-et-Ravageon ».

Du il est fait élection de domicile des opérations de liquidation.

Pour avis
La gérance

- CN 13896 -

Aux termes d'une assemblée générale ordinaire du 28 novembre 2001, les associés ont décidé d'immatriculer la société

S.C.I. AVENUE GALLINE

au registre du commerce et des sociétés.

Forme : Société civile immobilière.

Siège social : 55 bis, avenue Galline, 69100 Villeurbanne.

Objet : L'acquisition, l'administration, l'exploitation par bail, location ou autrement d'une usine à usage de pasteurisation du lait, autres constructions affectées à une église protestante, située à Villeurbanne (Rhône), 55 bis, avenue Galline.

Durée : Constituée le 23 mars 1951 pour une durée de 99 années.

Apports : 10 000 F en numéraire.

Capital social : 10 000 F, divisé en 1 000 parts de 10 F chacune.

Gérance : M. Alain CELLERIER demeurant à Lyon (69003), 133, rue Garibaldi.

Immatriculation : Au registre du commerce et des sociétés de Lyon.

Pour avis : la gérance

- SOC 13894 -

**RESTAURATION
HOTELLERIE
JPG CONSULTANT**

SARL au capital de 100 000 F
Siège social : 19, rue Claude-Veyron, 69007 Lyon
390 869 717 RCS Lyon

L'assemblée générale du 10 novembre 2001 a décidé de modifier la dénomination sociale de la société en

HORES CONSEIL

et de convertir le capital en 15 245 €, à compter du 31 décembre 2001.

Le dépôt légal est effectué au RCS de Lyon.

- SOC 13782 -

MVB

société anonyme au capital de 250 000 F
Siège social : 10, place Charles-Béraudier
69428 Lyon cedex 3
429 685 506 RCS Lyon

Aux termes d'une délibération en date du 2 mai 2001, l'assemblée générale ordinaire a nommé Monsieur Michel BOURGEAT, demeurant 3, chemin de Grave, 69450 Saint-Cyr-au-Mont-d'Or, en qualité de nouvel administrateur de la société, pour une période de 6 ans qui prendra fin à l'issue de l'assemblée générale ordinaire des actionnaires à tenir dans l'année 2007 pour statuer sur les comptes de l'exercice clos le 31 mars 2007.

Aux termes d'une délibération en date du 18 mai 2001, le conseil d'administration a nommé Monsieur Michel BOURGEAT, administrateur de la société, demeurant 3, chemin de Grave, 69450 Saint-Cyr-au-Mont-d'Or, aux fonctions de président du conseil d'administration de la société, pour une période de 6 ans, correspondant à la durée de son mandat d'administrateur.

Pour avis
Le conseil d'administration

- SOC 13854 -

LIPHA SA

société par actions simplifiée au capital de 77 797 247 €
Siège social : 37, rue Saint-Romain, 69008 Lyon
572 028 033 RCS Lyon

Des délibérations de l'assemblée générale extraordinaire du 7 décembre 2001, il résulte :

1) Que la société a été transformée de société anonyme en société par actions simplifiée, sans création d'un être moral nouveau, avec adoption de nouveaux statuts, à compter du 7 décembre 2001.

2) La modification des mentions suivantes à publier :

Anciennes mentions | Nouvelles mentions

FORME

Société anonyme.

Société par actions simplifiée.

ADMINISTRATION ET DIRECTION

Président et administrateur : M. Jean-Noël TREILLES.

Directeurs généraux :

M. André MEYNAUD

M. Yves BONHOMME

Administrateurs :

M. le Docteur Johannes SOMBROEK

M. le Docteur Michaël RÔMER

M. le Professeur Docteur Bernhard SCHEUBLE.

Président : M. Jean-Noël TREILLES, domicilié 37, rue Saint-Romain, Lyon 8^e.

Directeurs généraux :

M. André MEYNAUD, domicilié 37, rue Saint-Romain, Lyon 8^e.

M. Yves BONHOMME, domicilié 37, rue Saint-Romain, Lyon 8^e.

Conseil de surveillance :

M. Gérard MENU, domicilié 37, rue Saint-Romain, Lyon 8^e.

M. Marc HEIMERMANN, domicilié 37, rue Saint-Romain, Lyon 8^e.

Commissaires

aux comptes :

- Titulaire : KPMG DÉPARTEMENT FIDUCIAIRE DE FRANCE, 45, rue Villers, 92200 Neuilly-sur-Seine.

- Suppléant : SCP Jean-Claude ANDRE ET ASSOCIÉS, 2 bis, rue de Villiers, 92200 Levallois-Perret.

Commissaires

aux comptes :

- Titulaire : KPMG DÉPARTEMENT FIDUCIAIRE DE FRANCE.

- Suppléant : SCP Jean-Claude ANDRE ET ASSOCIÉS.

Agrement : Les cessions d'actions, même entre associés, sont soumises à l'agrement préalable de la collectivité des associés.

Dépôt au greffe du Tribunal de commerce de Lyon.

Pour avis
Le représentant légal

- SOC 13715 -

SARL HIPPOSOFT

société à responsabilité limitée en liquidation au capital de 50 000 F
Siège social : 22, rue Joliot-Curie
69320 Feyzin
392 497 947 RCS Lyon.

Suivant délibération d'une assemblée générale ordinaire du 14 décembre 2001, les associés, après avoir entendu le rapport du liquidateur, ont approuvé les comptes de liquidation, ont donné quitus au liquidateur, l'ont déchargé de son mandat puis ont prononcé la clôture des opérations de liquidation.

Les comptes de liquidation seront déposés au greffe du Tribunal de Commerce de Lyon.

Pour avis, le liquidateur

EXHIBIT 4

6071

MERCK SANTE

Simplified Joint-Stock Company ["Société par Actions
Simplifiée"] with a capital of € 77,797,247
REGISTERED OFFICE at 69008 Lyons

37, rue Saint-Romain

572 028 033 LYONS COMMERCIAL AND COMPANIES
REGISTER

In accordance with decisions of the sole shareholder dated 27
May 2002, the following amendments to the declarations to be
published were decided, from 1 July 2002:

Company name

Previous declarations :

LIPHA SAS.

New declarations :

MERCK SANTE.

Managing director

Previous declarations :

(Resignation on 1 June 2002).

Mr. Yves BONHOMME.

New declarations :

(Appointment on 1 July 2002).

Mr. Pierre-Henry LONGERAY

whose legal address is 37, rue
Saint-Romain, 69008 Lyons.

Notice hereby given

*The above English
translation is correct.
J. Millan Miller*

BEST AVAILABLE COPY

6071

MERCK SANTE

Société par Actions Simplifiée
au capital de 77 797 247 €
SIEGE SOCIAL à 69008 LYON
37, rue Saint-Romain
572 028 033 RCS LYON

Suivant décisions de l'associé unique en date du 27 mai 2002, il a été décidé les modifications suivantes des mentions à publier, et ce à compter du 1^{er} juillet 2002 :

Dénomination sociale

Anciennes mentions :	Nouvelles mentions :
LIPHA SAS.	MERCK SANTE.

Directeur Général

Anciennes mentions :	Nouvelles mentions :
(Démission au 1 ^{er} juin 2002).	(Nomination au 1 ^{er} juillet 2002).
M. Yves BONHOMME.	M. Pierre-Henry LONGERAY domicilié 37, rue Saint-Romain, 69008 Lyon.

Pour avis :

6072

MERCK SA

Société Anonyme
au capital de 20 058 176 €
SIEGE SOCIAL à 69008 LYON
37, rue Saint-Romain
777 335 340 RCS LYON

Suivant décisions de l'assemblée générale mixte du 18 mai 2002, il a été décidé les modifications suivantes des mentions à publier, et ce à compter du 1^{er} juillet 2002 :

Dénomination sociale

Anciennes mentions :	Nouvelles mentions :
MERCK LIPHA.	MERCK SA.

Et suppression du sigle LIPHA.

Pour avis :

6157

AMIS

Société à Responsabilité Limitée
au capital de 7 622,45 €
SIEGE SOCIAL à 69230 SAINT-GENIS-LAVAL
Chemin du Favier, Parc des Aqueducs
393 147 145 RCS LYON

L'assemblée générale extraordinaire du 29 mars 2002 a décidé de transférer le siège social à La Motte Servolex (73290), 109, rue de la Curiaz à compter du 1^{er} avril 2002 et modifié en conséquence l'article 4 des statuts.

Par assemblée générale ordinaire du 29 mars 2002, les associés ont nommé en qualité de gérant à compter du 1^{er} avril 2002 : M. Régis DEVOS demeurant 109, rue de la Curiaz, 73290 La Motte Servolex, en remplacement de M. Guillaume GRENIER, démissionnaire.

RCS Lyon.

6069

SOCIETE DE PARTICIPATION PHARMACEUTIQUE SA

Société Anonyme
au capital de 187 500 €
SIEGE SOCIAL à 69008 LYON
59, rue Villon
403 592 777 RCS LYON

Suivant délibérations de l'assemblée générale ordinaire des actionnaires en date du 11 juin 2002, il a été décidé les modifications suivantes des mentions à publier :

Administrateurs

Anciennes mentions :	Nouvelles mentions :
MERCK-LIPHA.	MERCK GENERICS FRANCE HOLDING SA, ayant son siège social 37, rue Saint-Romain, 69008 Lyon, représentée par M. Didier BARRET.

Commissaire aux comptes suppléant

Anciennes mentions :	Nouvelles mentions :
M. Louis BERTIATO.	M. Arnaud SCREVE, domicilié 3, avenue Général Brosset, 69160 Tassin-la-Demi-Lune.

Le conseil d'administration du même jour a choisi de conférer la direction générale de la société au Président du conseil d'administration, Monsieur Gérard MENU.

6265

GROUPE JURIS

Avocats
2, rue de la Claire, 69009 Lyon

GETRONICS-DECAN

Société Anonyme
au capital de 15 000 000 €
SIEGE SOCIAL à 69370 SAINT-DIDIER-AU-MONT-D'OR
Télébase, 6, avenue Claude Chappe
352 051 981 RCS LYON

Des procès-verbaux du conseil d'administration du 14 mai 2002 et de l'assemblée générale ordinaire annuelle du 28 juin 2002, il résulte les modifications suivantes des mentions à publier :

CONSEIL D'ADMINISTRATION

Ancienne mention :	Nouvelle mention :
Président : Adam DAVENPORT.	Président : Adam DAVENPORT.
Administrateur et Directeur Général Délégué : Laurent PITEK (*).	Administrateurs : DECAN GROUPE, représentée par Jean VERDOT.
DECAN GROUPE, représentée par Jean VERDOT.	René PIT demeurant Tasselschadestraat 4 1814 EK Alkmaar NETHERLANDS.
Douglas BERWICK SCOTT (**).	

(*) Démission avec effet au 31 décembre 2001.

(**) Démission avec effet au 5 avril 2002.

Pour avis :
LE PRESIDENT

6217

Maitre SMIDA Najet
Avocat à Vaux-en-Velin

AVIS DE CONSTITUTION DE SAS PLURIPERSONNELLE

Suivant acte sous seings privés en date du 12 juin 2002, il a été constitué une société présentant les caractéristiques suivantes :

Forme : Société par Actions Simplifiée.

Dénomination :

GIVORS ENTRETIEN ET SERVICES AUTOMOBILES

Capital : 38 320 €.

Siège social : 103, rue Jean Ligonnet, 69700 Givors.

Objet : La société a pour objet, en France et à l'étranger, la réparation rapide automobile, activité de garage : vidange, mise au point, petit entretien, achat-vente et pose de tous accessoires pour automobile, la vente de carburant, les opérations de lavage et de location de véhicules.

Durée : 99 ans.

Admission aux assemblées et droit de vote : Tout associé peut participer aux assemblées sur justification de son identité et de l'inscription en compte de ses actions. Chaque associé disposant d'autant de voix qu'il possède ou représente d'actions.

Inaliénabilité des actions : Les actions sont inaliénables au profit d'un tiers de la société pour une durée de dix ans à compter de leur souscription ou de leur acquisition.

Agrément : Les actions ne peuvent être cédées à des tiers étrangers à la société même entre actionnaires, qu'avec l'agrément de la collectivité des associés.

Président : Monsieur Yves GABRIEL, demeurant 115, chemin des Vieures, 69126 Brindas.

Commissaires aux comptes :

Titulaire : Monsieur Xavier BOUSQUET, demeurant 5, avenue Edouard Millaud, BP 49, 69290 Craponne.

Suppléant : SARL CAUDIREX, dont le siège est 5, avenue Edouard Millaud, BP 49, 69290 Craponne.

Immatriculation : La société sera immatriculée au Greffe du Tribunal de Commerce de Lyon.

6126

GIRCA

Entreprise Unipersonnelle à Responsabilité Limitée
au capital de 7 622,45 €
SIEGE SOCIAL à 69001 LYON
23, rue Royale
381 409 387 RCS LYON

Par décision de l'associé unique en date du 29 mars 2002, il résulte la modification suivante des avis antérieurement publiés :

Capital social :

- ancienne mention : 7 622,45 euros.

- nouvelle mention : 327 830,58 euros.

Les statuts ont été modifiés en conséquence.

Pour avis :
LA GERANCE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :

Yves BONHOMME et al.

Group Art Unit: 1615

Serial No.: 10/329,426

Examiner: Susan T. Tran

Filed: December 27, 2002
U.S. Patent No. 6,303,146

For: SOLID ORAL DOSAGE FORM COMPRISING A COMBINATION OF
METFORMIN AND GLIBENCLAMIDE

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Name: A. J. ZELANO

Signature: [Signature]

Date: 11/20/03 (Sph)

I, Geoffrey L. Nicholson, being duly warned, hereby declare as follows.

32 pp (attachment)

1. I am a co-inventor of the above-identified application and am a former Director of Pharmaceutical Development for Lipha Pharmaceuticals, UK, a wholly owned subsidiary of the assignee of this reissue application, Merck Sante of Lyons, France. I have a financial interest in this application in that I receive certain remuneration based on sales of products covered by its claims, and I have been compensated on an hourly basis for my time in preparing this declaration.

2. My curriculum vitae is attached.

3. I have read the Office Action of October 22, 2003.

4. The invention which my co-inventors and I made involved a problem we discovered regarding the bioavailability of glibenclamide when it is formulated in a single dosage form, e.g., tablet, along with metformin. Single dose combinations of glibenclamide and metformin were known prior to our invention (e.g., as the Examiner has mentioned based

on WO 97/17975 (Barelli), Suguan M, and others). The idea behind such single dosage forms was to provide a more convenient treatment regimen for patients who are taking both drugs separately. It was presumed that the bioavailability of the two active ingredients from a single tablet is comparable to that of the two active agents co-administered in different dosage forms.

5. We discovered that this presumption was not true for dosage forms prepared according to the prior art, containing a combination of metformin and commercially available bulk glibenclamide. Whereas the single dose bioavailability of metformin was comparable to the separately administered version, that of glibenclamide was not. We have discussed this general problem in our U.S. Patent 6,303,146, at column 1, lines 54-59, column 2, lines 4-22, column 2, lines 41-44, etc. We concluded that the prior art did not "teach how to formulate a combination product of metformin with glibenclamide so as to assure appropriate bioavailability of the glibenclamide component" (column 1, lines 60-63). Thus, patients were not receiving the plasma concentration profile which was presumed, as explained at col. 5, lines 8 – 20 of US'146. We demonstrated the nature of the problem in Figures 2 and 3 of USP '146 and the accompanying text. Basically, these figures show that if one employs commercially available bulk glibenclamide and co-formulates with metformin, the plasma concentration curve of the combination tablet (open circles of Figure 2) establishes a glibenclamide bioavailability which is not comparable to that of the separately co-administered drugs (closed circles of Figure 2), e.g., an AUC (area under the curve) of 353.0 vs. an AUC of 869.3, respectively (col. 4, lines 49 – 57). On the other hand, when appropriate attention is given to how to formulate the drugs in a single dosage form, the bioavailabilities of glibenclamide are comparable between the combination tablet ("x" of Figure 3) and the separately co-administered drugs (open circles of Figure 3), e.g., an AUC of 790.5 vs. an AUC of 869.3, respectively (col. 4, lines 49 – 57). Thus, if one employs conventionally

available bulk glibenclamide without any consideration of how to formulate it with metformin in a single dosage form in order to achieve such comparable bioavailability for the glibenclamide, for instance as Barelli does (page 17, lines 4-10), one will not achieve the comparable bioavailability demonstrated in USP '146.

6. Further demonstrating the lack of such comparable bioavailability for glibenclamide in the prior art, we analyzed prior art commercially available single dosage forms containing both metformin and glibenclamide with respect to their dissolution profiles of glibenclamide. We performed side-by-side comparison experiments of these prior art dosage forms against a tablet of this invention prepared according to col. 6, lines 30-49 of US'146 except adjusted for dosage as indicated below. All the prior art dosage forms disclosed in Table I on page 4 of Barelli were tested, including Suguan M mentioned by the Examiner. See attached Figure A.

7. All dissolution data shown in Figure A were measured by the Blume Method (Drug Dev & Ind Pharmacy, 19(20), 2713-2741 (1993)). A copy is attached. Blume dissolution data are reasonably correlated with bioavailability. Thus, products which are markedly differentiated in their Blume in vitro dissolution properties can reliably be expected to exhibit therapeutically relevant differences in bioavailability as indicated in the Summary of the Blume article. The Blume Method is also useful as a quality control tool to confirm bioavailability which has previously been demonstrated by in-vivo studies in man. Its reliability is fully supported by the fact that several international regulatory authorities have accepted the Blume method as a valid quality control tool in the regulatory dossiers for Glucovance (TM), a product covered by the claims of this application.

8. The doses of glibenclamide and metformin in the tested tablets are as stated in Table I of Barelli, i.e., 2.5 mg of glibenclamide in each case except for Bi-euglucon M5 which has 5 mg of glibenclamide. The tablet of this invention also had 2.5mg of

glibenclamide, and had 500 mg of metformin. Other tablets of this invention having 5 mg/500mg and 1.25mg/250mg of glibenclamide/metformin have been shown to have Blume dissolution curves sufficiently the same as that shown in Figure A that quality control limits for regulatory purposes using Blume curves are the same for all these dosages. Precise amounts of each ingredient in a tablet will affect absolute plasma concentrations achieved in patients but not the Blume curve, as discussed in the preceding sentence. This is because Blume curves measure a relative parameter, i.e., percent dissolution, which normalizes for the absolute amount in the tablet. The Blume method thus permits comparisons of even different strength tablets. Blume data are truly comparative for the purpose of demonstrating dissolution profile differences, and thus as discussed herein, corresponding bioavailability differences.

9. As can be seen from Figure A, Suguan M and all of the other conventional formulations have glibenclamide release profiles which are significantly different from that of this invention. This strongly supports that their in vivo bioavailabilities are also different from that of this invention. It can therefore be inferred from the Blume data that because our invention has comparable glibenclamide bioavailability to the separately administered drugs, the tested prior art formulations do not have such comparable bioavailability because their release profiles shown in Fig. A are so different from that of this invention. Thus, the Examiner's contrary assumption for Suguan M and the other prior art is incorrect, i.e., they do not have the same chemical composition and formulation as this invention and do not have the same properties as this invention. These data on all the commercial formulations disclosed in Table I of Barelli establish that one, following Barelli and using commercially available glibenclamide, would not achieve the current invention.

10. The Examiner points out a statement on page 2 of the package insert for Suguan M that its glibenclamide is virtually 100% bioavailable and achieves a C_{max} from 2 to

6 hours after administration. This simply means that virtually 100% of the drug reaches the plasma at some time which requires that virtually 100% of the drug is dissolved, as is also shown by the Blume data in Fig. A, and that a maximum concentration is reached in the 2 - 6 hour range. However this says little about "bioavailability" in the context here, i.e., the nature of the plasma concentration curve, showing the rate and extent of entry into the bloodstream (e.g., col. 2, lines 7 - 9 of US '146 and its Example 2), and little about whether such bioavailability is comparable to that when metformin and glibenclamide are administered in different dosage forms.

11. The foregoing establishes that the combination tablets of this invention possess an unexpected significant advantage over the prior art tablets, i.e., a glibenclamide bioavailability comparable to that of glibenclamide when it is co-administered with metformin.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

19th November 2003
date


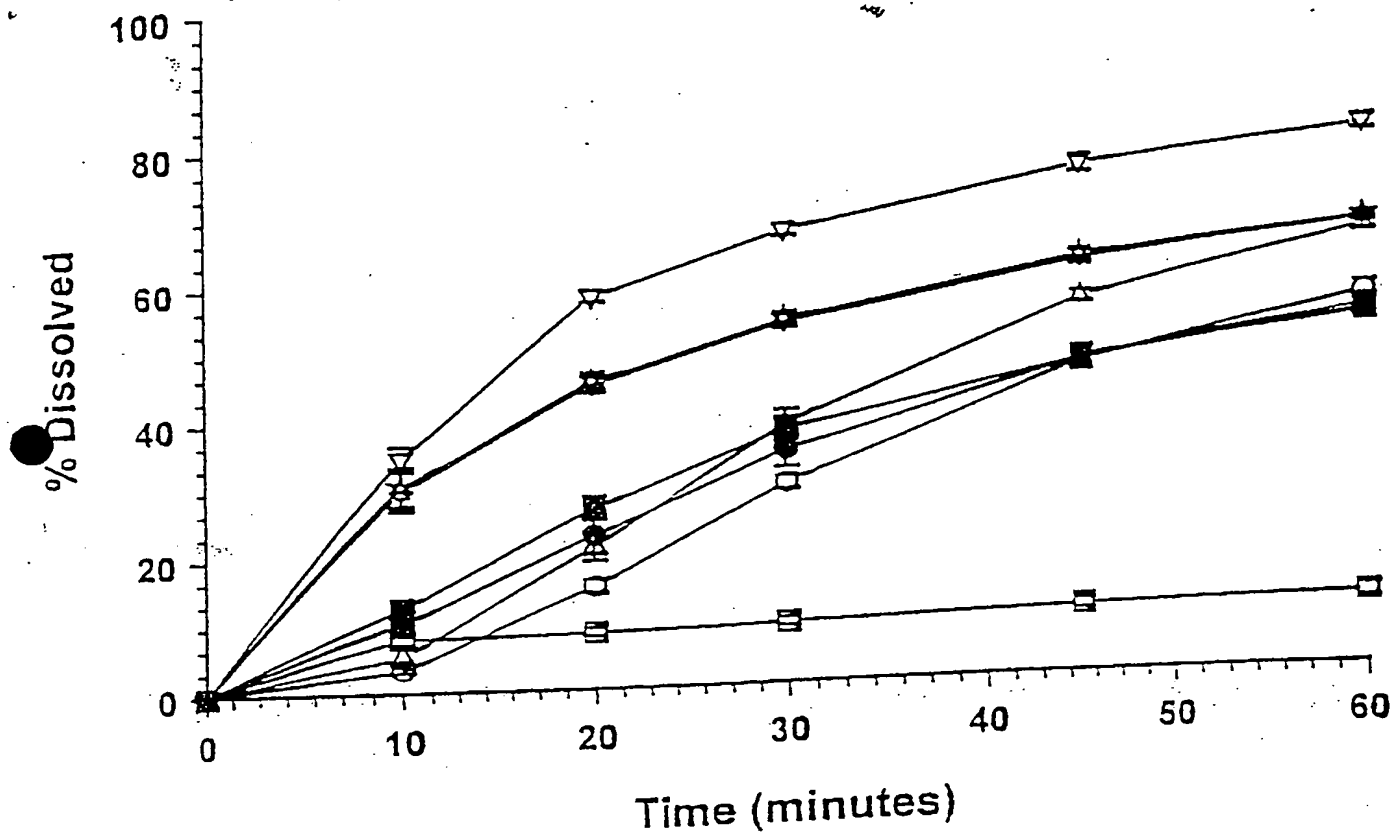

Geoffrey L. Nicholson

Fig.A Graph to show comparison of Glyburide dissolution data (Blume Method) for metformin/glyburide combination competitor products



- ▽ Tablets prepared in accord with present invention
- ◇ Suguan M tablets
- ★ Suguan M tablets
- △ Glibomet tablets
- Glibomet tablets
- Glucomide capsules
- Bi-euglucon M5
- Bi-euglucon M

CURRICULUM VITAE

Geoffrey L Nicholson

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60 years young with 18 years as Director of Merck Pharmaceutical Development Centre, Hitchin, which I created, equipping the premises and recruiting key professional staff. I designed the laboratories, specified and purchased capital items and set up effective links with universities and consultant/service groups.

MSc., C Chem., MRSC and Registered 'Qualified Person'. PC literate using Microsoft Office and other software. I had frequent international travel and contact by telephone or email and have fluent French plus basic German. An international decision to end development in the UK mean that I had to manage a phased site closure until the end of September 2003 when I took early retirement.

Career History

1985 to 30/9/03 Merck (formerly Lipha) Pharmaceuticals Ltd.

Director of Pharmaceutical Development

Reporting (up to end 2001) to the Director General R&D Ethicals, based in Lyon, France and since then to the Head of Global Pharmaceutical Development at Merck HQ in Germany.

I managed all aspects of our product development programme, co-ordinated, organised and managed senior staff, set and controlled budgets and allocated resources. We prepared Clinical Trials supplies for the international clinical programme and by delegation I ensured we met all statutory requirements. I had frequent contact with a wide range of specialist technical service providers and Regulatory Authorities, both UK and Europe/US based.

Main responsibilities

To develop products (both new chemical entities and life cycle management) which comply with international regulatory requirements and provide a real benefit to patients.

To be responsible for the effective management of the people, resources and budgets of the Development Centre.

To provide a Centre of Excellence to the Merck Group in pharmaceutical development.

1980 – 1985 Leo Laboratories Limited

Head of Pharmaceutical Development and Quality Control

Reported to UK managing Director and Group R&D Director with full budgetary and resource allocation authority.

- set up new facility
- chaired committee to design factory, sterile production unit and laboratories
- recruited technical staff, specified and purchased capital equipment

1973 - 1980 Reckitt and Colman Pharmaceuticals Division

Section Manager reported to Pharmaceutical Development Manager with responsibility for formulation of ethical and OTC medicinal products, control of pilot plant and Production department troubleshooting.

1962 - 1973 various roles progressing from Assistant Chemist to Section Leader in QC and R&D laboratories

Qualifications

MRSC - Member of The Royal Society of Chemistry 1970

C. Chem – Chartered Chemist 1970

MSc. (Pharmaceutics) 1971 Chelsea College, University of London

Courses

Numerous management training and specialist technical courses have been taken to maintain current awareness of international requirements.

Additional Information.

Married. Non-smoker, in good health.

Active local Methodist Church member: (Pastoral visitor, Circuit Treasurer and Transport Officer former Senior Steward).

Keen weekend golfer (member at Chiltern Forrest GC)